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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,233	01/16/2007	Fabrizio Giannotta	FLGDK29.002APC	4530

20995 7590 06/09/2009

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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	**PAPER NUMBER**
1652	

NOTIFICATION DATE	DELIVERY MODE
06/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/589,233	GIANNOTTA ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12,15-23 and 25* is/are pending in the application.

4a) Of the above claim(s) *8-11 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7, 12 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *SEQ ALIGN*.

Detailed Action
Election/Restriction

Applicant's election with traverse of Group I, claims 1, 4-12 and 15-23 with respect to SEQ ID NO: 2 and the heterologous nucleotide sequence of SEQ ID NO: 25 and as species "(i) being a specific partner for any polypeptide or ligand", for prosecution in their response dated 03/06/09 is acknowledged. The traversal is on the grounds that "the Office alleges the restriction between Group I and Group II is proper because shared technical features of claims, the polynucleotides and polypeptides does not contribute over prior art… and applicants submit that both groups of claims share a corresponding technical feature that is neither anticipated nor rendered obvious by the cited reference WO 03/105753".

Applicants' arguments have been considered, however examiner respectfully disagrees for the following reasons. 1) Searching structurally distinct molecules like polypeptides and the polynucleotides are not coextensive and involves search of different databases and non-patent literature, as prior to the concomitant isolation and expression of the sequence of interest there may be scientific journal articles devoted solely to the polypeptides which would not have described the polynucleotide and moreover the polypeptides may have been isolated by biochemical means from natural source or generated by peptide synthesis methods as opposed to the expression of polypeptide through recombinant methods. 2) In addition, Group I and II, polynucleotides and encoded polypeptides encompasses molecules which are claimed in terms of mutants and variants of β-lactamase of SEQ ID NO: 2 and protein A of *Staphylococcus aureus* of SEQ ID NO: 25 (for details see 112 second paragraph and

112 first paragraph rejections below), therefore, the breadth and the scope of the claims are very broad that involves search of different sequence databases and analysis of results. Furthermore, the cited reference WO 03/105753 when combined with prior art indeed renders the instant invention obvious (for details see 103 (a) obviousness rejection below). In addition, as cited in the Office action dated 03/06/09 (Requirement for Restriction), the PCT does not provide for multiple products or methods within single application, therefore, unity of invention is lacking with regard to Groups I-II; see 37 CFR 1.475. 37 CFR 1.475 (d) also states: If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) 1.47(c). 3) Applicants' request to rejoin the withdrawn polypeptide claims (Group II) with elected polynucleotide of Group I is not being considered at this stage of prosecution.

Therefore, for the above cited reasons searching of all variants of SEQ ID NO: 2, SEQ ID NO: 25 including the encoded polypeptides is a serious search burden and contrary to applicant's arguments, the requirement is still deemed proper and is therefore made FINAL.

Claims 1, 4-12, 15-23 and 25 are pending in this application, Group I, claims 1, 4-7, 12 and 15-23 with respect to SEQ ID NO: 2 and the heterologous nucleotide sequence of SEQ ID NO: 25 and as species "(i) being a specific partner for any polypeptide or ligand" are now under consideration for examination. Please note that

claims 8-11 are also withdrawn as they read on non-elected invention (class C and D β-lactamase); thus claims 8-11 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/06/08.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). This application is a 371 of PCT/EP05/50174 filed on 01/17/2005 and claims the priority date of EPO application 04075430.1 filed on 02/11/2004. Examiner notes that the certified copy of said EPO application has been provided.

Information disclosure statement

The information disclosure statement (IDS) submitted on 08/10/06 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS has been considered and initialed by the examiner.

Abstract- Objection

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Specification-Objections
Informalities

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 4, 7, 12 and 21 are objected to, due to the following informality: Claims 14, 7, 12 and 21 recite the abbreviation "TEM-1" in the claims. Examiner suggests expanding the abbreviation to recite the full form of what the abbreviation stands for at least in the first recitation of said abbreviation. Appropriate correction is required.

Claim Rejections 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6, line 2 recites the phrase "derived from class A β-lactamase". It is not clear to the examiner as to what the phrase "...derived from..." means in the context of the above claim, is this synonymous with "obtained from specific strain or source" or does it include natural and man-made mutants thereof from any source. Furthermore, literally while the term "derived" means to "to isolate from or obtain from a source", the above term could also mean "to arrive by reasoning i. e., to deduce or infer" or also mean "to produce from another substance". It is noted that while the term "derived from" will encompass genes encoding class A β-lactamase naturally found in any microorganism or cells, the term in its broadest reasonable interpretation will also encompass any variant artificially created gene encoding class A β-lactamase from any microorganism or cell, wherein said enzyme has the recited bio-chemical

properties. Since a gene and encoded protein activity is defined by its structure, if a man-made variant of said gene encoding said enzyme has similar structure (i. e., polynucleotide and encoded amino acid sequence) and bio-chemical properties as that of a gene encoding a protein isolated from any source, the term "derived from…" would not allow one of skill in the art to differentiate between these genes and encoded proteins, especially the claim language recites no defined structure and can potentially read on many variant structures/genes encoding variant polypeptides having class A β-lactamase activity. Therefore, unless applicant has defined the term "derived…" as equivalent to "obtained from the specific source with specific structure", the term "derived from…" does not further limit the recited polynucleotide and encoding enzyme. Clarification and correction is required.

Claims 21 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 21 and 23 recite the phrase "…hybridizes under stringent conditions…", but does not recite conditions under which the hybridization must occur. In the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination and nucleic acids which hybridize under one set of conditions may not hybridize under other conditions. It is not clear to the examiner as to what type of stringent conditions are encompassed in the above phrase. Thus the scope of the claim is unclear. Examiner was unable to find any support following perusal of the specification for hybridization conditions. As such it is unclear how homologous or identical to the nucleotide

sqeuence of SEQ ID NO: 2 and SEQ ID NO: 25, a claimed sequence must be to be included within the scope of the claims. Clarification and correction is required

Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claim 1 and claims 4-7, 12 and 15-23 depending therefrom are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant nucleotide sequence which codes upon expression a bifunctional hybrid class A β-lactamase encoded by the polynucleotide sequence of SEQ ID NO: 2, wherein said class A β-lactamase protein is bearing a heterologous protein A from *Staphylococcus aureus* encoded by the polynucleotide sequence of SEQ ID NO: 25, wherein said class A β-lactamase protein is bearing the heterologous protein A from *Staphylococcus aureus* in a region located between the region forming a juncture between alpha helix 8 and alpha helix 9. However, specification does not reasonably provide enablement for any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide

sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claim.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 4-7, 12 and 15-23, broadly encompass any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any

undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the structure of the polynucleotides and encoded proteins with desired biological function i.e., any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function.

The disclosure is limited to a recombinant nucleotide sequence which codes upon expression a bifunctional hybrid class A β-lactamase encoded by the polynucleotide sequence of SEQ ID NO: 2, wherein said class A β-lactamase protein is bearing a heterologous protein A from *Staphylococcus aureus* encoded by the polynucleotide sequence of SEQ ID NO: 25, wherein said class A β-lactamase protein is bearing the heterologous protein A from *Staphylococcus aureus* in a region located between the region forming a juncture between alpha helix 8 and alpha helix 9, but

provides no guidance with regard to the making of variants, mutants and recombinants i.e., any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function. In view of the great breadth of the claims, amount of experimentation required making the claimed polynucleotides and encoding polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (for example, see Whisstock et al., Prediction of protein function from protein sequence and structure. Q Rev Biophys. 2003, Aug. 36 (3): 307-340. Review), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polynucleotides and encoded polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claim, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a

reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function as in claims 1, 4-7, 12 and 15-23, because the specification does not establish: (A) regions of the polynucleotide/protein structure which may be modified without affecting the activity of encoded β-lactamase enzyme or heterologous protein, *Staphylococcus aureus* protein A; (B) the general tolerance of the polypeptide having β-lactamase enzyme activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the

desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function as in claims 1, 4-7, 12 and 15-23. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides and encoded polypeptides having the desired biological characteristics and the use of the same is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 1, 4-7, 12 and 15-23 (as interpreted), are directed to any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case the scope of the instant claims encompass a genus of structures (no structural limitation) for encoded polynucleotides and polypeptides of interest, i.e., any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function.

While the specification discloses the structure and the use of a recombinant nucleotide sequence which codes upon expression a bifunctional hybrid class A β-lactamase encoded by the polynucleotide sequence of SEQ ID NO: 2, wherein said class A β-lactamase protein is bearing a heterologous protein A from *Staphylococcus aureus* encoded by the polynucleotide sequence of SEQ ID NO: 25, wherein said class A β-lactamase protein is bearing the heterologous protein A from *Staphylococcus aureus* in a region located between the region forming a juncture between alpha helix 8 and alpha helix 9, the specification is silent in regard to (1) the structures of all the polynucleotides and encoded polypeptides encompassed by the claims, (2) the critical

structural elements of any variant, mutant or recombinant β-lactamase protein from any source and having associated function.

The genus of polypeptides required in the claimed invention is an extremely large, functionally and structurally variable genus. While the argument can be made that the recited genus of polynucleotide and encoded polypeptides are adequately described by the disclosure of the structure of the polynucleotide sequence of SEQ ID NO: 2 and SEQ ID NO: 25, since one could use structural homology to isolate other polynucleotides and encoding polypeptides having the claimed function, as taught by the art, even highly structurally homologous polypeptides do not necessarily share the same function and many functionally similar proteins will have little or no structural homology to disclosed proteins. For example, proteins having similar structure have different activities; Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures.

Therefore, the claimed genera of polynucleotides and encoded polypeptides include widely variable structures, since minor structural changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polynucleotides and encoded polypeptides are encompassed by these claims. The specification only discloses a few species/structures of the recited genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-7, 12 and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al., (WO 03/105753, in IDS) in view of Balint et al., (US 2003/0165825 A1), Galarneau et al., (Nature Biotechnology, 2002, Vol. 20: 619-622, in

IDS), Neugebauer et al., (Nucleic Acids Res., 1981, Vol. 9 (11): 2577-2588) and Finck-Barbancon et al., (FEMS Microbiol. Lett., 1992, Vol. 70 (1): 1-8).

Claims 1, 4-7, 12 and 15-23 are directed to any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function.

Murray et al., (*supra*) teach methods and compositions (polynucleotides and encoding polypeptides) for grafting functional loops into a protein, including β-lactamases (page 19, line 19; pages 25-26) and placement of heterologous sequences in said β-lactamase that are surface accessible and not part of secondary structure including region spanning L184-K193 of β-lactamase enzyme (page 56, line 16-25; pages 66-67, Example 1).

Balint et al., (*supra*) teach break point termini for β-lactamase wherein heterologous proteins can be conjugated (polynucleotide encoding heterologous

proteins) and said β-lactamase fragments bearing the heterologous proteins are enzymatiaclly active as they functionally reassemble to form catalytically active enzymes, specifically break point regions Glu197/Leu198 that can be utilized to conjugate any heterologous protein of interest (Abstract, Fig. 1, 3 and 4, paragraphs [0020-0024]) and suggest an exposed loop of β-lactamase between the amino residues Thr195 to Ala202, between helixes 7 and 8 (paragraph [0049], α197 (N-terminal fragment) and ω198 (C-terminal fragment) and said fragments cooperatively produce selectable activity (enzyme activity) in a manner that is strictly dependent on specific interactions between heterologous domains fused to the break-point termini of the β-lactamase (paragraph [0050]; Examples 1-12, paragraphs [0079-0164]).

Similarly, Galarneau et al., (*supra*), also teach the β-lactamase structure and dissection of the enzyme between Gly196 and leu198, because this site is located on a surface opposite the active site and produces fragments of approximately the same length, it also contains no periodic structure and it is topologically feasible for the protein to fold and the use of said fragments in a protein fragmentation assay (PCA), i.e., when reconstituted said fragments attain the proper topology (higher order structure) to be catalytically active. Said reference also demonstrates successful fusion of various proteins to said fragments of β-lactamase to detect protein-protein interactions via protein fragmentation assay (page 619, column 2, second paragraph; Fig. 2; page 620, Fig.1A-1B; and entire document).

Neugebauer et al., (*supra*) teach the isolation of *Bacillus licheniformis* polynucleotide sequence encoding the β-lactamase having 100% homology to SEQ ID

NO: 2 of the instant invention (see provided sequence alignment).

Finck-Barbancon et al., (*supra*) teach the isolation of Staphylococcus aureus polynucleotide sequence encoding the protein A having 97% sequence homology (best local similarity) to SEQ ID NO: 25 of the instant invention (see provided sequence alignment).

Therefore, it would have been obvious to a person of ordinary skill in the art to modify the combined teachings of Murray et al., Balint et al., and Galarneau et al., that discloses optimal regions in a β-lactamase for fusing any heterologous sequence/protein of interest, the predicted 3-D structures, higher order topology and the specific amino acid residues that form active residue sites and helixes and hence Murray et al., Balint et al., and Galarneau et al., provide all the guidance required for one skilled in the art as derived in the instant invention i.e., any polynucleotide sequence encoding a bifunctional hybrid protein wherein said bifunctional hybrid protein comprises: i) any or all β-lactamase and its variants, mutants and recombinants of undefined structure from any or all sources; ii) encoded by any polynucleotide sequence of SEQ ID NO: 2 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 2; iii) said β-lactamase protein of undefined structure bearing a heterologous protein located between any two neighboring alpha helices such as alpha helix 8 and alpha helix 9, said alpha helix 8 and alpha helix 9 is selected from the group consisting of the amino acid sequence of Thr195 to Leu199 of the alpha helix 8 and alpha helix 9 TEM-1 β-lactamase or the amino acid sequence corresponding to the amino acid sequence of

Thr195 to Leu199 of the alpha helix 8 and alpha helix 9 TEM-1 β-lactamase and having biological function and further said heterologous protein encoded by polynucleotide sequence of SEQ ID NO: 25 of any length (fragments) and its variants of undefined structure hybridizing under any undefined stringent conditions to SEQ ID NO: 25 and having protein A activity or biological function.

Motivation to do so derives from the fact that the use of β-lactamase as a reporter molecule and as a carrier molecule in the production fusion proteins comprising various heterologous peptides and polypeptides of interest are well established in the art. One of ordinary skill in the art would have a reasonable expectation of success, since β-lactamase structures (polynucleotide sequence as taught by Neugebauer et al.,), said β-lactamase engineered to comprise genes encoding structures of interest in well defined regions of β-lactamase and retaining the enzymatic function are also well known in the art (Murray et al., Balint et al., and Galarneau et al.,).

Therefore, claims 1, 4-7, 12 and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al., (WO 03/105753, in IDS) in view of Balint et al., (US 2003/0165825 A1), Galarneau et al., (Nature Biotechnology, 2002, Vol. 20: 619-622, in IDS), Neugebauer et al., (Nucleic Acids Res., 1981, Vol. 9 (11): 2577-2588) and Finck-Barbancon et al., (FEMS Microbiol. Lett., 1992, Vol. 70 (1): 1-8).

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims,

Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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